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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 09/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,039	WILLIAMS, JAMES A.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *25-31* is/are rejected.

7)☐ Claim(s) *25,28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/5/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 have been canceled; New Claims 25-31 have been submitted.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 25, 27 and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2-5,9,12-14, 24,28 (in light of the definition provided for targeting ligand comprising an amino acid component at col. 6, lines 57-62 and col. 45-65 that is the C-terminal heavy chain) and claim 31 of U.S. Patent No. 6,787,517. Although the conflicting claims are not identical, they are not patentably distinct from each other because the allowed claims are directed to a species of invention of the instantly claimed genus of toxin agents that comprise a light chain, an Hn portion and an Hc . While the instant claims recite the term recombinant, the allowed agents are defined to include recombinantly produced portions from a gene that codes for each portion (see allowed claim 37, col. 37, line 2 "gene", as well as recombinantly produced portions defined through out US Pat. #6,787,517). The allowed species anticipates the instantly claimed genus of botulinum toxins.

Claim Objections

1. Claim 25 and 28 are objected to because of the following informalities:

2. Claim 25 is directed to a recombinant toxin set forth in the following general format:

A or B, heavy chain, C or D and E or F.

Claim 25 does not clearly define what combinations of the recombinant toxin portions are intended to be combined in light of the format of the claim reciting three "or" phrases and one "and" phrase. Additionally, on line three of the claim a "," comma appears after the term "G, " and before the term "heavy chain"; the presence of a "," comma after G and before the term "heavy chain" appears to define a distinction between the portions set forth before the term "heavy chain". What is the source of the C-terminal portion, as the recited botulinum toxin types have C-terminals for the light and heavy chains? The location of the comma set forth in the claim after the letter "G" adds confusion.

Claim 28 recites the phrase "wherein the toxin is in a solution"; the claim should recite the phrase ----further comprising----, or claimed as a composition comprising the toxin and a solution.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 25-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 25-31 all recite the phrase "C-terminal portion" and "an N-terminal

portion". The portions are not defined in the claims to evidence any specific biological function, and therefore read on a single amino acid portion of the entire N- and C-terminal amino acid sequences. The invention as now claimed reads on a light chain together with two additional amino acids, one each for the C- and N-terminal portions. How can the N-, and C-terminal portions be distinguished from the non-toxin protein sequence, when a single amino acid portion can be from any source and be considered to be from the toxin or non-toxin? What sequence distinguishes the toxin portion sequence from the non-toxin sequence of amino acids? While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

Claim Rejections - 35 USC 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002

do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Please Note: In light of the claimed invention requiring the recombinant botulinum toxin to comprise the recited portions the claimed toxins read on isolated complete botulinum toxins. Additionally the recitation of the term "recombinant" is being read as a process limitation, and the claimed toxin reads on the naturally occurring toxins absent claiming distinguishing characteristics that differ from that which occurs in nature, as no structural differences are encompassed by what is now claimed from that which would be present in an isolated botulinum toxin produced by natural sources.

6. Claims 25-26, 29-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Whelan et al (1992).

Whelan et al disclose botulinum toxins B, C, D and E, which comprise both L and H chain domains, to include the C-terminal and N-terminal amino acid sequences (see Whelan et al, pages 2350-2351, Figure 4) of the botulinum toxins heavy chains. The reference compares the nucleotide sequences that encode the botulinum toxins (see Table 1, page 2352) as well as the degree of homology between the various botulinum toxins. No distinguishing characteristics have been set forth in the claims to show that the claimed product by process "recombinant" limitation would not be the same or equivalent product obtained by a different process, specifically purified from natural sources. The disclosed botulinum toxins anticipate the instantly claimed invention.

7. Claims 25-26, 29-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Campbell et al (1997, SWISS-PROT accession number Q60393).

Campbell et al disclose botulinum toxin G, which comprise both L and H chain domains, to include the C-terminal and N-terminal amino acid sequences (see Campbell et al, amino acid sequence ledger) of the botulinum toxins heavy chains. No distinguishing characteristics have been set forth in the claims to show that the claimed product by process "recombinant" limitation would not be the same or equivalent heavy chain obtained by a different process, specifically purified from natural sources. The disclosed botulinum toxin G anticipates the instantly claimed invention.

8. Claims 25-26, 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Maisey et al (1988). The following rejection is being made in light of the C-terminal portion of a botulinum toxin may be any heavy chain based upon the fact that there is a comma after the term "G", which sets forth an additional species of any "heavy chain" which is combined with a botulinum toxin type B light chain.

Maisey et al disclose botulinum toxin B light chain (LC_B) combined with a heavy chain of a botulinum toxin (HC_A) , the heavy chain comprising both the N- and C- terminal portions (see Table 1, page 687 "chains renatured together" and "mixture of renatured chains", in solution). No distinguishing characteristics have been set forth in the claims to show that the claimed product by process "recombinant" limitation would not be the same or equivalent heavy chain obtained by a different process, specifically purified from natural sources. The disclosed botulinum toxin B, and botulinum toxin B chimera anticipate the instantly claimed invention.

9. Claims 25-29, 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Dolly et al (US Pat. 6,203,794, effective filling date May 31, 1994)

Dolly et al disclose the instant claimed invention directed to a recombinant botulinum neurotoxin (see Dolly et al, col. 2, lines 25-36), wherein the botulinum toxin is botulinum toxin B, C, D, E, F and G (see Dolly et al, col. 7, lines 18-30; col. 41, claims 2-3).

(Instant claims 25-26) The botulinum toxin comprises a light chain portion (see Dolly et al, col. 8, line 2; see Dolly et al, claims 1-3; col. 24, lines 62-65; Example 15), a heavy chain targeting portion and an internalizable portion (see Dolly et al, claim 4, and col. 5, lines 12-14) which are equivalent portions to the C-terminal and N-terminal functions of a botulinum heavy chain.

(Instant claim 27) The recombinant botulinum toxin is expressed using a maltose binding protein (see col. 17, lines 29-39) expression vector (see Dolly et al, for example: col. 3, lines 54-66) and would therefore evidence a specific solubility conferred by the expression vector fusion protein.

(Instant claim 28) The botulinum toxin is claimed as a pharmaceutical composition (see Dolly et al claim 4) and is in solution with a pharmaceutically acceptable excipient (see Dolly et al, col. 41, lines 66-67).

(Instant claim 29) The C-terminal and N-terminal portions of the heavy chain are linked one to the other (see Figure 1B) .

(Instant claim 31) The light chain and N-terminal of the heavy chain are bonded to each other (see figure 1B). No distinguishing characteristics have been set forth in the claims to show that the claimed product by process "recombinant" limitation would not be the same or equivalent heavy chain obtained by a different process, specifically purified from natural sources.

The botulinum toxin is disclosed to be mutated through the addition of a non-toxin sequence, specifically a "cysteine" at the N-terminal of the light chain (see Dolly et al, col. 12, lines 55-61). An additional embodiment disclosed is the expression of the recombinant light chain as a fusion protein that comprises "a non-toxin protein sequence" that is cleavable by Factor Xa (see Dolly et al col. 28, lines 59-64; figure 1A) or is a GST fusion protein (see Dolly et al, Example 21, col. 31).

Dolly et al anticipates the instantly claimed invention as now claimed.

Please Note: The following prior art rejection is being made over the claims based upon the recitation of "or" defining alternative embodiments together with a light chain based upon the recitation of the term "and".

10. Claims 25-31 are rejected under 35 U.S.C. 102(a) as being anticipated by WO94/21684.

WO94/21684 disclose the instantly claimed invention directed to a composition that comprises a peptide portion of the heavy chain H_N together with a light chain (see Example 1, page 7, L- H_N , the peptide evidencing an epitope present in botulinum toxin B, C and F (see Table 6, page 20). The C-terminal portion of the L-chain is covalently linked to the N-terminal portion of the heavy chain. The polypeptide portion is disclose to be in association with other non-toxin protein sequences, in a" conjugated or otherwise linked to other sequences" (see page 3, paragraph 4).

An additional embodiment disclosed comprises botulinum toxin heavy and light chains of serotypes B, C, D and E, the heavy chains comprising portions of both the H_N and H_C together with the N-terminal peptide that is held in common with serotypes B, C and F (see Table 6,

Expt. 2) and a solution (pharmaceutical excipient) carrier (see page 5, paragraphs 1-3 and claim 13-14).

No distinguishing characteristics have been set forth in the claims to show that the claimed product by process "recombinant" limitation would not be the same or equivalent heavy chain obtained by a different process, specifically purified from natural sources.

The reference anticipates the instantly claimed invention.

Conclusion

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

12. Dertzbaugh (US Pat. 6,287,566) is cited to show compositions that comprise protective portions and neutralizing portions of botulinum toxin light and heavy chains.

13. Montal et al (US Pat. 5,837,265) disclose modified B and E botulinum toxins that comprise both a light chain and a heavy chain, the heavy chain comprising both the N- and C-terminal portions (see col. Col. 7, lines 1-59; col. 8, lines 18-20 and claims 3, 7, 11 and 15). The modified toxins were formulated into a pharmaceutical composition and would therefore be in a solution, such as saline (see col. 8, line 51), or combined with a non-toxin protein sequence (see col. 9, lines 32-38 "polypeptides, proteins, amino acids" and lines 45-46).

14. Murphy (US Pat. 5,965,406) is cited to show hybrid botulinum neurotoxins (see all claims).

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on 7:30-5:00 M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
September 7, 2004

L. R. F. Smith

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